REMARKS

With entry of the present amendment, claims 1-3, 4-10, 12-16, 18, 22, 29-31 and 39-76 are pending. Claims 69-76 are new. Claims 3,11, 22-28 and 32-37 are hereby canceled. Claims 17, 19-21 and 38 were previously cancelled. Claims 1, 4, 12, 13, 22, 29-31, 40, 43, 44, 46, 48, 49, 51 and 53-59 are amended as is reflected in the listing of claims above. No new matter is believed to be presented by the foregoing amendments.

Claims 53, 55 and 57 are amended to correct the spelling of sulfate. The other claims are amended as further detailed below.

Entry of this amendment and reconsideration of the claims, as amended and in view of the following remarks, is requested.

Priority

The priority date of May 15, 2000 was denied as to claims containing methionine as an antioxidant as this was not one of the specifically itemized antioxidants listed in the priority application EP 00110355.5. The independent claims have been amended, inter alia, to remove methione and state instead "antioxidant." This language is supported for example at page 6 or priority document EP 00110355.5 and page 10 of the instant application. It is respectfully submitted that as amended, the independent claims are entitled to the priority date of May 15, 2000.

The specific antioxidant methionine appears in dependent claims 44, 45, 47, 54, 56, 58, 69, 74 and 75. Support for methionine as an antioxidant is found for example at page 10 of parent application USSN 09/853,731 as it was filed on May 11, 2001.

The 103 Rejections

Claims 1-5, 9-16, 18, 22-26, 30-39, 46-52 and 59 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bailon US Pat. No. 6,583,272 in view of Takuri US Pat. No. 5,272,135. This rejection is overcome.

Claims 3, 11, 23-28 and 32-37 are canceled. Claims 1, 2, 4, 5, 9-10, 12-16, 18, 22, 30-31, 39, 46-52 and 59, are amended to replace "methionine" with an "antioxidant" and to replace "multiple charged inorganic anion" with "sulfate, phosphate or citrate anion." Most of these claims are also amended to include a specific amount of the erythropoietin glycoprotein product. These amendments are supported by the priority document, for example at pages 6, 21 and 22, and are entitled to a priority date of May 15, 2000. These amendments are supported by the instant application, for example, at pages 4, 9, 10 and 27-29. As these claims are entitled to the priority date of May 15, 2000, for the reasons already of record in parent application USSN 09/853,731, the disclosure in the Bailon '272 patent that relates to formulations (namely Example 8) is not a proper reference against these claims.

On its face, the record in the parent application (USSN 09/853,731) of the instant application shows that Example 8 was first added to the application that resulted in the Bailon '272 patent in June 2000, which is after the priority date of the instant application and of the currently presented independent claims. As such, this portion of the '272 patent is not prior art against these claims.

Claims 1-16, 18, 22-39, 46-52 and 59 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Bailon US Pat. No. 6,583,272 in view of Sato US Patent No. 6,908,610 (corresponding to WO 00/51629). This rejection is also overcome.

Claims 3, 11, 23-28 and 32-37 are canceled. Claims 1, 2, 4, 5-10, 12-16, 18,22, 30-31, 39, 46-52 and 59, amended as described above, are entitled to a priority date of May 15, 2000. For the reasons already of record in parent application USSN 09/853,731 and as discussed above, Example 8 of the '272 patent is not prior art against these claims.

For the foregoing reasons, the rejections under Section 103 are overcome and should be withdrawn.

Obviousness-Type Double Patenting

Claims 1-16, 18, 22-37 and 39-68 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 24, 25, 27-34, 38-42, 51-55, 59-61, 67, 68 71-77 and 83-108 of co-pending application USSN 09/853,731 (CD 20619 US). Neither the current application nor the '731 application have allowed claims. Moreover, applicant notes that on September 19, 2005, a terminal disclaimer over the instant application (CD 20619 US1) was already filed in USSN 09/853,731. As such, applicant submits that the request for another terminal disclaimer is improper or at least premature.

Supplemental Information Disclosure Statement

In the Supplemental Information Disclosure Statements dated February 13, 2006 and January 17, 2006, applicant brought to the Examiner's attention the fact that oppositions were launched against European Patent EP 1 311 285, which corresponds to the instant application. Further to the foregoing Supplemental Information Disclosure Statements, applicant submits herewith and bring to the Examiner's attention a copy of the response filed to these oppositions by the patentee on August 3, 2006.

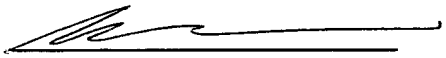
CONCLUSION

The foregoing amendment is fully responsive to the Office Action dated March 17, 2006. Applicants submit that claims 1-3, 4-10, 12-16, 18, 22, 29-31 and 39-76, as amended, are allowable. Early and favorable consideration is earnestly solicited.

If the Examiner believes there are other issues that can be resolved by telephone interview, or that there are any informalities remaining in the application which may be corrected by Examiner's Amendment, a telephone call to the undersigned attorney is respectfully solicited.

Applicants submit herewith a request for a three month extension of time and the appropriate fee. Should the Patent Office determine that an additional fee is owed, or a credit is due to applicant, the Patent Office is hereby authorized to charge any required fees, including any extension of time and/or excess claim fees, or credit any overpayment, to applicant's Deposit Account 08-2525 as appropriate.

Respectfully submitted,



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IHR ZEICHEN / YOUR REF.	UNSER ZEICHEN / OUR REF.	DATUM / DATE
	37670P EP/WWkd	- 3. Aug. 2006

Application/Patent No:
1 311 285
Applicant/Proprietor:
F. Hoffmann-La Roche AG
Opponent: Sandoz AG, Neose Technologies Inc., BioGeneriX AG

Encls
Consolidated list of documents (Enclosure 1)
Amended claim 45 (Enclosure 2)
Auxiliary Request (Enclosure 3)

(copies for OI, OII and OIII)

This is in response to the communication dated 30 January 2006.

1. Requests

Oppositions have been filed against the European Patent EP 1 311 285 (Patent in Dispute) by Sandoz AG (OI), Neose Technologies Inc. (OII) and BioGenerix AG (OIII).

Please find enclosed a consolidated list of documents presented by the Opponents as Enclosure 1.

It is requested to maintain the Patent in

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Postbank München
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S.W.I.F.T.-Adresse **PBNKDEFF 700**

Dispute based on claims 1-44 and 46-51 as granted and an amended claim 45 as enclosed (Enclosure 2)). Auxiliarily, it is requested to maintain the patent based on claims 1-48 of the Auxiliary Request (Enclosure 3).

Further, Oral Proceedings are auxiliarily requested.

2. Amended Claims

In amended claim 45, the backreference has been amended from "claims 1-44" to "claim 44". Claims 1-44 and 46-51 remain as granted.

In claim 1 of the Auxiliary Request, the multiple charged inorganic anion is specified as sulphate. Thus, claim 1 of the Auxiliary Request is a combination of claims 1 and 6 as granted.

Claims 2-48 of the Auxiliary Request correspond to claims 2-3 and 7-51 as granted. In claim 42 of the Auxiliary Request (corresponding to claim 45 as granted), the backreference has been amended from "claims 1-44" to "claim 41".

Finally, in claim 46 of the Auxiliary Request, the multiple charged anion has been specified as sulphate in accordance with claim 1.

3. Subject-matter of the Patent in Dispute

3.1 Subject-matter of the Main Request

Claim 1 of the Patent in Dispute (Main Request) refers to a liquid pharmaceutical composition comprising a pegylated human erythropoietin protein, a multiple charged inorganic anion in a pharmaceutically acceptable buffer suitable to keep the solution pH in the range from 5.5 to 7.0, and optionally one or more pharmaceutically acceptable excipients, said liquid composition being stable at room temperature.

Claims 2-48 refer to preferred embodiments of the composition of claim 1.

Claim 49 refers to a process for preparing a composition according to any of claims 1 to 48, comprising mixing a pegylated human erythropoietin protein with a solution comprising a multiple charged anion and optionally one or more pharmaceutically acceptable excipients and adjusting the pH to 5.5 to 7.0 using a pharmaceutically acceptable buffer.

Claim 50 refers to the use of a composition according to any of claims 1 to 48 for the preparation of medicaments useful for the treatment and prevention of diseases correlated with anemia in chronic renal failure patients (CRF), AIDS and/or for the treatment of cancer patients undergoing chemotherapy.

Finally, claim 51 refers to a device for local and systemic sustained release comprising a composition accordance to any of claims 1 to 48 selected from the group consisting of an implant, a syringe and an inhalation device.

The Patent in Dispute is based on the invention that pegylated human erythropoietin compositions are stabilised by providing a multiple charged inorganic anions in a pharmaceutically acceptable buffer with a pH in the range of 5.5 to 7.0.

Thus, the technical features of claim 1 are as follows:

(1) liquid pharmaceutical composition

(2) pegylated human erythropoietin

(3) multiple charged inorganic anion

(4) pharmaceutically acceptable buffer

(5) pH in the range of 5.5 to 7.0

(6) stable at room temperature.

3.2 Subject-Matter of the Auxiliary Request

According to claim 1 of the Auxiliary Request, the multiple charged inorganic anion is further specified as sulphate.

As will be explained in the following, the subject-matter of the Patent in Dispute fulfils the requirements of the European Patent Convention.

4. New Matter (Art. 123(2) EPC)

4.1 Claim 1

The Opponents allege that the subject-matter of the Patent in Dispute contains new matter with regard to the originally filed application WO 01/87329 and thus does not fulfil the requirements of Art. 123(2) EPC.

With regard to claim 1, it is argued that the feature "stable at room temperature" is not supported in the specification as filed. Further, it is argued that a combination of the features "pegylated erythropoietin" and "stable at room temperature" cannot be found in the original application.

Patentee submits that the Opponent's arguments are unfounded. The original application WO 01/87329 (p. 3, lines 21-26 corresponding to paragraph [0008] of the patent as granted) reads as follows:

"It has been surprisingly found that formulating an erythropoietin in this composition improves its stability at temperatures above refrigerator temperature (2-8°C), especially at room temperature (i.e. below 25°C) and even at higher temperatures, e.g. 40°C. This means that the composition can be stored without cooling for a prolonged period of time, without losing significant amounts of activity and without significant degradation."

This passage provides sufficient basis for the feature of granted claim 1 that the liquid composition is stable at room temperature, in that the compound can be stored without cooling for a prolonged period of time.

Further, it is submitted that there is a clear correlation between the terms "pegylated erythropoietin" and "stability at room temperature". In this context, it is referred to WO 01/87329, p. 4, lines 23-29. It is stated therein that the term "erythropoietin" refers to human erythropoietin and analogues which are defined below, namely "pegylated erythropoietins". Thus, there is a clear correlation between both features. Consequently, the subject-matter of claim 1 is supported by the originally filed documents.

4.2 Claims 34, 45 and 46

Further, the Opponents allege that claims 34, 45 and 46 contain new matter. This objection particularly refers to the backreference of these claims. Claims 34 and 46 refer to a composition comprising the 10 mM sodium phosphate, 40 mM sodium sulphate, 3% (w/v) mannitol, 1 mM methionine pH 6.2. First, the Applicant would like to point out that Example 11 of the Application as filed (p. 42, Table 4 and legend thereof) discloses a "formulation C" comprising the ingredients as defined in claims 34 and 46. Additionally, it is indicated in the following paragraph of the specification (p. 42, lines 15-20) that a preferred formulation of the present invention (10 mM sodium phosphate, 40 mM sodium sulphate, 3% (w/v) mannitol pH 6.2) may be supplemented with 1 mM methionine. The indication of this formulation as a "preferred formulation of the present invention" is sufficient basis for a generic disclosure allowing a combination with the features of other embodiments of the application as filed. Thus, the backreferences of claims 34 and 46 do not constitute new matter.

With regard to claim 45, the Patentee has amended the backreference only to claim 44. Thus, the Opponent's objections have become moot.

4.3 Specification

The Opponent OIII alleges that the description has been indadmissibly broadened by inserting the term "pegylated" in several passages of the patent. As pointed out above, the WO publication explicitly discloses that the term "erythropoietin" covers "pegylated human erythropoietin". Thus, the insertion of the term "pegylated" does not represent new matter.

5. Sufficiency of Disclosure (Art. 83 EPC)

The Opponents allege that the subject-matter of the Patent in Dispute is not sufficiently disclosed and thus does not fulfil the requirements of Art. 83 EPC. These objections particularly refer to the term "stable at room temperature".

The Patentee submits that the Patent in Dispute provides sufficient disclosure for the skilled person in order to determine if a composition is "stable at room temperature". In this context, it is referred to paragraph [008] of the patent as granted stating that the composition can be stored without cooling for a prolonged period of time without losing significant amounts of activity and without significant degradation.

First, it should be noted that the Opponents have not provided any substantive evidence that the determination of stability and bioactivity of pegylated EPO was not possible or did require undue burden for the skilled person at the priority date. For this reason alone, the Opponent's allegations must fail.

In contrast, the determination of the activity of erythropoietin and measurements for determining the stability of proteins were well-known at the priority date. Thus, the skilled person was able to determine the stability of a pharmaceutical composition comprising a pegylated human erythropoietin protein as an active ingredient. Further, the determinations of activity and stability are explicitly described in the Examples of the Patent in Dispute.

Example 13 describes the determination of pegylated EPO after storage at

elevated temperature, e.g. at room temperature for prolonged time periods, namely 6 months. The results shown in Figure 10 demonstrate that a formulation comprising pegylated EPO in 10 mM sodium phosphate, 40 mM sodium sulphate, 3% (w/v) mannitol, pH 6.2 does not show a significant loss of activity after storage at 25°C for 6 months.

Example 10 of the Patent in Dispute describes a determination of the stability of pegylated EPO in various formulations at different temperatures including room temperature of 25°C. Based on the test results shown in Example 10 of the Patent in Dispute, the skilled person can assess the stability of any given formulation without undue burden.

Thus, in contrast to the case underlying the decision T749/98, the Patent in Dispute provides a clear and unambiguous teaching which is used to determine activity and stability of the claimed compositions. The Patent clearly identifies the means by which to assess its claimed property.

Thus, the subject-matter of the Patent in Dispute fulfils the requirements of Art. 83 EPC.

6. Novelty (Art. 54 EPC)

6.1 General Remarks

The Opponents allege that the subject-matter of the Patent in Dispute lacks novelty in view of several prior art documents. Patentee submits that none of the cited documents contains a novelty-destroying disclosure for the subject-matter of the claims on file.

6.2 WO 00/61169 (D1)

D1 refers to pharmaceutical compositions of erythropoietin stabilized with an amino acid and a sorbitan derivative. The document has been published on 19 October 2000 and thus represents prior art only in the sense of Art. 54(3) EPC

for the subject-matter of the Patent in Dispute insofar as it is covered by the priority. The document does not disclose a specific example of a liquid pharmaceutical composition comprising a pegylated human erythropoietin protein. Further, there is no direct and unambiguous disclosure in the general part of the specification for a formulation comprising all features of claim 1 of the Patent in Dispute. Particularly, there is no disclosure of an EPO composition comprising sulphate anions.

6.3 EP-A-1064951 (D2)

D2 was published on 3 January 2001 and thus is prior art only in the sense of Art. 54(3) EPC. The document refers to compositions comprising a pegylated EPO. In Example 4, samples comprising unpegylated EPO or pegylated EPO were diluted with BSA-PBS and tested in an *in vivo* assay. There is, however, no disclosure with regard to the pH of the resulting formulation. Thus, Example 4 is not novelty-destroying for the subject-matter of claim 1 of the Patent in Dispute. Particularly, the document does not disclose the presence of sulphate anions in an EPO formulation.

6.4 WO 01/02017 (D3)

D3 was published on 11 January 2001 and thus is prior art only in the sense of Art. 54(3) EPC. The document discloses pegylated EPO derivatives. On page 19, lines 8-10, it is stated that the compounds may be formulated in 10 mM sodium/potassium phosphate buffer at pH 7 containing a tonicity agent, e.g. 132 mM sodium chloride. There are, however, no data indicating that the formulation is stable at room temperature. Thus, there is no clear and unambiguous disclosure of all features of claim 1 of the Patent in Dispute. Particularly, there is no disclosure for incorporating sulphate anions into an EPO composition.

6.5 WO 01/017542/EP-A-1 232 753 (D4)

D4 was published on 15 March 2001 and thus is prior art only in the sense of

Art. 54(3) EPC. The document refers to stable protein solution formulations filled in a container made from a hydrophobic resin at least for the part in direct contact with the formulation. The Examples do not describe any formulation comprising a pegylated EPO. D4 also does not describe any individual embodiment which directly and unambiguously discloses a pharmaceutical composition having all features of claim 1 of the Patent in Dispute. Particularly, there is no disclosure or suggestion to incorporate sulphate anions into an EPO formulation.

6.6 WO 98/05363 (D5)

D5 was published before the priority date of the Patent in Dispute and thus is prior art in the sense of Art. 54(2) EPC. The document refers to polypeptides conjugated with a water-soluble polymer. Pegylated proteins are disclosed on page 19, lines 17-23. EPO is disclosed as a preferred polypeptide on page 13, line 15. There is, however, no disclosure of a buffer with multiple charged anions having a pH according to claim 1 of the Patent in Dispute. Particularly, there is no disclosure that sulphate anions might be incorporated into the formulation.

6.7 WO 01/76640 (D13)

D13 was published on 18 October 2001 and thus represents prior art only in the sense of Art. 54(3) EPC. Example 1 describes a pegylated EPO-NESP conjugate which is diluted with 20 mM sodium phosphate, 150 mM NaCl, pH 7.2 from a size exclusion chromatographic column. The pH of this composition is clearly outside the scope of claim 1 of the Main Request, which requires a pH 5.5 to 7.0. Thus, this document is clearly irrelevant for the subject-matter of claim 1 of the Patent in Dispute. Particularly, there is no disclosure to incorporate sulphate anions into an EPO formulation.

6.8 US Patent 5,354,934 (D15)

D15 describes EPO compositions for pulmonary administration. The document

does not exemplify a formulation of pegylated EPO at all. Further, there is no clear and unambiguous disclosure to employ formulations of pegylated EPO having the features of claim 1 of the Patent in Dispute. Particularly, there is no disclosure to incorporate sulphate anions into an EPO formulation.

6.9 EP 1,260,230/WO01/064241 (D16)

D16 was published for the first time on 7 September 2001 and thus represents prior art only in the sense of Art. 54(3) EPC. The document does not disclose a formulation comprising pegylated EPO as an active ingredient. Further, the general description of the document does not directly and unambiguously disclose a formulation of pegylated EPO having the features of claim 1 of the Patent in Dispute. Particularly, D16 does not contain any disclosure at all with regard to the presence of sulphate anions.

6.10 EP-A-1 336 410/WO02/011753 (D24)

D24 is based on a first priority of 4 August 2000 (JP 2000237432), which is after the priority date of the Patent in Dispute. Thus, D24 can only be regarded as prior art for the subject-matter of the Patent in Dispute not covered by its priority and insofar as the subject-matter of D24 is covered by its own priority document JP 254 89 699. Opponent OIII, however, has not submitted a copy of this priority document. Thus, the novelty attack based on D24 has not been substantiated.

D24 refers injectable protein preparations with a pH of 6.5 to 7.4 and comprising at least one sugar. Formulations containing pegylated erythropoietin are not exemplified. Further, the general part of the specification does not contain any direct and unambiguous disclosure for a pharmaceutical composition having all features of claim 1 of the Patent in Dispute. Particularly, there is no disclosure for incorporating sulphate anions into the formulation.

7. Inventive Step (Art. 56 EPC).

7.1 General remarks

The Opponents allege that the subject-matter of the Patent in Dispute is not based on an inventive step. Patentee submits that the Opponent's objections are unjustified as will be explained in detail below.

6.2 The Invention

According to the Patent in Dispute, a stable formulation of pegylated human erythropoietin is provided. The formulation is stable at room temperature. In order to provide a stable pharmaceutical formulation of pegylated human erythropoietin, the Patentee has carried out experiments as shown in the Examples of the Patent in Dispute. Based on these experiments, it was surprisingly found that pegylated human erythropoietin is stabilised by multiple charged anions in a pharmaceutically acceptable buffer at a pH in the range of 5.5 to 7.0.

The subject-matter of the Patent in Dispute is inventive over the prior art. The skilled person would not have reasonable expectation of success that a liquid pharmaceutical composition comprising a pegylated human EPO and a multiple charged inorganic anion in a pharmaceutically acceptable buffer at a pH from 5.5 to 7.0 could be stable at room temperature.

First, it should be noted that the results in the prior art referring to unpegylated human EPO cannot be transferred to pegylated human EPO. The solubility and stability characteristics of EPO change fundamentally by means of pegylation. Thus, the skilled person could not draw any reasonable conclusions from data obtained with unpegylated EPO if he/she was facing the problem of providing a stable liquid pharmaceutical composition of pegylated human EPO.

Further, the excellent stability of liquid pharmaceutical compositions comprising a multiple charged inorganic anion compared to other compositions comprising

glycine, arginine and succinate could not have been expected by the skilled person. Thus, the subject-matter of claim 1 of the Patent in Dispute is based on an inventive step.

Particularly, none of the cited prior art documents does suggest that the addition of sulphate anions into a liquid pharmaceutical composition comprising pegylated human EPO as an active ingredient would provide an increased stability as shown in the Examples of the Patent in Dispute. In this context, particular reference is made to Figure 6 of the Patent in Dispute, wherein a formulation comprising 150 mM phosphate pH 6.2 is compared to a composition comprising 10 mM phosphate and 140 mM sulphate pH 6.2. As shown in Figure 6, the sulphate-containing formulation has a significantly higher transition temperature indicating a high stability. This high stability of sulphate containing formulations is confirmed in Example 10 (cf. Table 3: formulations B, D and E) as well as in Example 13 (cf. Fig. 10) and Example 14 (cf. Fig. 11).

Thus, it is concluded that the prior art documents do not provide any indication that the addition of multiple charged anions, particularly sulphate anions, to a liquid pharmaceutical composition comprising human pegylated EPO would improve its properties. Thus, the subject-matter of the Patent in Dispute is based on an inventive step.

7. Summary

The subject-matter of the Patent in Dispute fulfils the requirements of the European Patent Convention. Thus, the request for dismissing the oppositions and maintaining the Patent in Dispute are justified.

Dr W Weiß

	Dokument	*OI*	*OII*	*OIII*
D1	WO 00/61169	D1	D3	D11
D2	EP 1 064 951	D2	D8	D7
D3	WO 01/02017	D3		D5
D4	EP 1 232 753	D4	D5	D10
D5	WO 98/05363	D5		
D6	EP 0 909 564	D6	D7	D5a
D7	GB 2 171 304	D7		
D8	EP 0 456 153	D8		D13
D9	EP 0 539 167	D9		D14
D10	Austria-Codex 1998/99	D10		
D11	WO 94/28024	D11		
D12	WO 95/11924	D12		
D13	WO 01/76640		D1	D3
D14	US 09/545,335		D1a	D4
D15	US 5,534,934		D2	
D16	EP 1 260 230		D4	D9
D17	US 5,661,125		D6	
D18	WO 01/87239			D1
D19	EP 00 110 355.5			D2
D20	WO 98/58660			D5b
D21	WO 99/07401			D5c
D22	US 60/142,243			D6
D23	US 60/142,254			D8
D24	EP 1 336 410			D12
D25	Rote Liste 2000, excerpts referring to Erypo® (Janssen-Cilag, No. 08047), NeoRecormon® (Roche, No. 08048)			D15

European Patent No. 1 311 285
37670P EP/WWkd

Amended claim 45

1. The composition of claim 44 comprising 10 mM sodium phosphate, 40 mM sodium sulfate, 3% mannitol, 10 mM methionine, 0.01% pluronic F68, pH 6.2.

European Patent No. 1 311 285
37670P EP/WWkd

Auxiliary Request: Claims 1-48

1. A liquid pharmaceutical composition comprising a pegylated human erythropoietin protein, a multiple charged inorganic anion in a pharmaceutically acceptable buffer suitable to keep the solution pH in the range from 5.5 to 7.0, and optionally one or more pharmaceutically acceptable excipients, said liquid composition being stable at room temperature, wherein the anion is a sulfate anion.

2. The composition according to claim 1 which is an aqueous solution.

3. The composition according to claims 1 to 2 which is an isotonic solution.

4. The composition according to claim 1 comprising 10 to 200 mmol/l sulfate.

5. The composition according to claims 1 to 4 wherein the pH is 5.8 to 6.7.

6. The composition according to claim 5 wherein the pH is 6.0 to 6.5.

7. The composition according to claim 6, wherein the pH is about 6.2.

8. The composition according to claims 1 to 7 wherein the buffer is selected from the group consisting of a phosphate or an arginine/H_2SO_4/Na_2SO_4 buffer.

9. The composition according to claim 8 wherein the buffer is a 10 to 50 mmol/l phosphate buffer.

10. The composition according to claims 1 to 9 wherein the composition comprises one or more pharmaceutically acceptable excipients.

11. The composition according to claim 10 wherein one or more pharmaceutically acceptable excipients are selected from the group consisting of pharmaceutically acceptable salts, diluents, solvents and preservatives.

12. The composition according to claims 10 and 11 wherein the pharmaceutically acceptable excipients are selected from the group consisting of tonicity agents, polyols, anti-oxidants and non-ionic detergents.

13. The composition according to claims 10 to 12 wherein the pharmaceutically acceptable excipient is a polyol.

14. The composition according to claim 13 wherein the polyol is selected from the group consisting of mannitol, sorbitol, glycerol, trehalose and saccharose.

15. The composition according to claim 14 wherein the polyol is mannitol.

16. The composition according to claims 10 to 15 comprising an anti-oxidant.

17. The composition according to claim 16 wherein the anti-oxidant is methonine.

18. The composition according to claims 10 to 17 comprising up to 1 mmol/l $CaCl_2$.

19. The composition according to claims 12 to 18 wherein the non-ionic

detergent is polysorbate 80, polysorbate 20 or pluronic F68.

20. The composition according to claim 19 wherein the non-ionic detergent is pluronic F68.

21. The composition according to claims 19 or 20, wherein the composition comprises up to 1 % (w/v) of the non-ionic detergent.

22. The composition according to any of claims 19 to 21, wherein the composition comprises up to 0.1 % (w/v) of the non-ionic detergent.

23. The composition according to any of claims 1 to 22, wherein the erythropoietin protein is a conjugate, said conjugate comprising a human erythropoietin glycoprotein, said glycoprotein being covalently linked to "n" poly(ethylene glycol) groups of the formula $-CO-(CH_2)_x-(OCH_2CH_2)_m-OR$ with the -CO of each poly(ethylene glycol) group forming an amide bond with one of said amino groups; wherein R is lower alkyl; x is 2 or 3; m is from about 450 to about 900; n is from 1 to 3; and n and m are chosen so that the molecular weight of the conjugate minus the erythropoietin glycoprotein is from 20 kilodaltons to 100 kilodaltons.

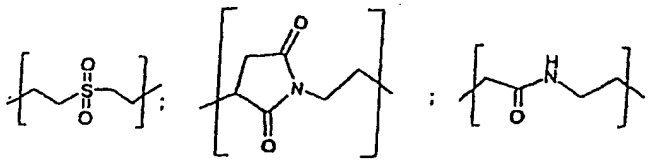
24. The composition according to claim 23 with an erythropoietin protein of the formula:

$$P-[NHCO-(CH_2)_x-(OCH_2CH_2)_m-OR]_n \qquad I$$

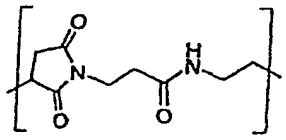
wherein m, n, x and R are as above, and P is the residue of the glycoprotein without the n amino group(s) which form amide linkage(s) with the poly(ethylene glycol) group(s).

25. The composition according to claim 24, wherein in formula (I) x is 2, m is 650 to 750, n is 1 and R is methyl.

26. The composition according to any of claims 1 to 22, wherein the erythropoietin protein is a conjugate, said conjugate comprising a human erythropoietin glycoprotein, said glycoprotein being covalently linked to from one to three lower-alkoxy poly(ethylene glycol) groups, each poly (ethylene glycol) group being covalently linked to the glycoprotein via a linker of the formula -C(O)-X-S-Y- with the C(O) of the linker forming an amide bond with one of said amino groups, X is $-(CH_2)_k-$ or $-CH_2(O-CH_2-CH_2)_k-$, k is from 1 to 10, Y is

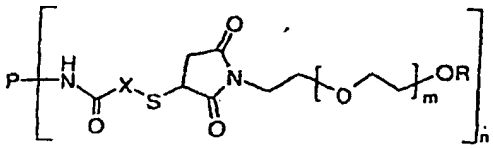


or



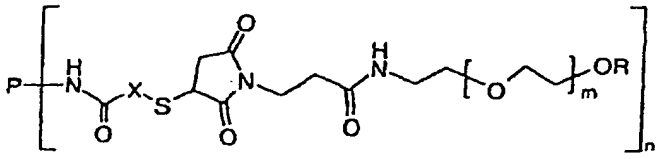
the average molecular weight of each poly(ethylene glycol) moiety is from about 20 kilodaltons to about 40 kilodaltons, and the molecular weight of the conjugate is from about 51 kilodaltons to about 175 kilodaltons.

27. The composition of claim 26, wherein the erythropoietin protein is a conjugate of the formula:



wherein n is an integer from 1 to 3; m is an integer from 450 to 900; R is lower alkyl; X is $-(CH_2)_k-$ or $-CH_2(O-CH_2-CH_2)_k-$, and P is the residue of the erythropoietin glycoprotein without the amino group or groups which form an amide linkage with X.

28. The composition of claim 27, wherein the erythropoietin protein is a conjugate of the formula:



wherein n is an integer from 1 to 3; m is an integer from 450 to 900; R is lower alkyl; X is $-(CH_2)_k-$ or $-CH_2(O-CH_2-CH_2)_k-$, and P is the residue of the erythropoietin glycoprotein without the amino group or groups which form an amide linkage with X.

29. The composition of claims 1 to 28 comprising 10 µg to 10000 µg erythropoietin protein per ml.

30. The composition of claims 1 to 29 comprising 10 µg to 10000 µg erythropoietin protein per ml, 10 - 200 mmol/l sulfate, and 10 to 50 mmol/l phosphate pH 6.0 to 6.5.

31. The composition of claims 1 to 30, comprising 10 mM sodium phosphate, 40 mM sodium sulfate, 3% (w/v) mannitol and 1 mM methionine, pH 6.2.

32. The composition of claim 30 or 31 comprising up to 20 mM methionine, 1 - 5 % of a polyol (w/v), up to 0.1 % pluronic F68 (w/v) and optionally up to 1 mM $CaCl_2$.

33. The composition according to claims 30 to 32 comprising 10 µg to 10000 µg erythropoietin protein per ml, 40 mmol/l sulfate, 10 mmol/l phosphate, 3% mannitol (w/v), 10 mM methionine, 0.01 % pluronic F68 (w/v), pH 6.2.

34. The composition according to claims 1 to 29, comprising 10 µg to 10000 µg erythropoietin protein per ml, 10 to 100 mmol/l NaCl, 10 to 50 mmol/l phosphate pH 6.0 to 7.0, optionally 1-5% of a polyol.

35. The composition of claim 34 comprising up to 20 mM methionine, up to 0.1 % pluronic F68 and optionally 7.5 µmol/l $CaCl_2$.

36. The composition of claim 34 or 35 comprising 10 µg to 10000 µg erythropoietin protein per ml, 100 mmol/l NaCl, 10 mM methionine, 0.01% pluronic F68, and 10 mmol/l phosphate, pH 7.0.

37. The composition of claims 1 to 29 comprising 10 µg to 10000 µg erythropoietin protein per ml, 10 to 50 mmol/l arginine, pH 6 to pH 6.5, 10 to 100 mmol/l sodium sulfate.

38. The composition of claim 37 comprising up to 20 mM methionine, up to 0.1 % pluronic F68, optionally up to 1 mmol/l $CaCl_2$ and optionally 1 - 5 % of a polyol.

39. The composition of claims 37 or 38, comprising 10 µg to 10000 µg erythropoietin protein per ml, 40 mmol/l arginine, pH 6.2, 30 mmol/l sodium sulfate, 3 % mannitol, 10 mM methionine, 0.01 % pluronic F68 and optionally 1 mmol/l $CaCl_2$.

40. The composition according to claims 1 to 29 comprising 25 to 2500 µg/ml erythropoietin protein and
a) 10 mM sodium/potassium phosphate, 100 mM NaCl, pH 7.0 or

b) 10 mM sodium phosphate, 120 mM sodium sulfate, pH 6.2 or

c) 10 mM sodium phosphate, 40 mM sodium sulfate, 3% mannitol, pH 6.2 or

d) 10 mM sodium phosphate, 40 mM sodium sulfate, 3% mannitol, 10 mM methionine, 0.01% pluronic F68, pH 6.2 or

e) 40 mM arginine, 30 mM sodium sulfate, 3% mannitol, pH 6.2 or

f) 40 mM arginine, 30 mM sodium sulfate, 3% mannitol, 10 mM methionine, 0.01% pluronic F68, pH 6.2.

41. The composition of claims 1 to 40 wherein the amount of erythropoietin protein is 50, 100, 400, 800 or 2500 µg/ml.

42. The composition of claim 41 comprising 10 mM sodium phosphate, 40 mM sodium sulfate, 3% mannitol, 10 mM methionine, 0.01% pluronic F68, pH 6.2.

43. The composition of claim 41 comprising 10 mM sodium phosphate, 40 mM sodium sulfate, 3% (w/v) mannitol, 1 mM methionine, pH 6.2.

44. The composition of claim 41 comprising 40 mM arginine, 30 mM sodium sulfate, 3% mannitol, 10 mM methionine, 0.01 % pluronic F68, pH 6.2.

45. The composition according to claims 1 to 44, wherein the erythropoietin protein has the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2.

46. A process for preparing a composition according to any of claims 1 to 45, comprising mixing a pegylated human erythropoietin protein with a solution comprising a multiple charged anion and optionally one or more pharmaceutically acceptable excipients and adjusting the pH to 5.5 to 7.0 using a pharmaceutically acceptable buffer, wherein the anion is a sulfate anion.

47. Use of a composition according to any of claims 1 to 45 for the

preparation of medicaments useful for the treatment and prevention of diseases correlated with anemia in chronic renal failure patients (CRF), AIDS and/or for the treatment of cancer patients undergoing chemotherapy.

48. Device for local and systemic sustained release comprising a composition according to any of claims 1 to 45 selected from the group consisting of an implant, a syringe and an inhalation device.